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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/316,199	05/21/1999	Michael J McCluskie	C1040/7006HC	7506

7590 05/08/2008

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EXAMINER	
POPA, ILEANA	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
05/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/316,199	MCCLUSKIE ET AL.	
	Examiner	Art Unit	
	ILEANA POPA	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-9,12,13,15-20,22,25-28,129,135-142 and 144-146* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/02/2007 has been entered.

Claims 2, 3, 10, 11, 14, 21, 23, 24, 29-128, 130-134, and 143 have been cancelled. Claim 136 has been amended.

Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are pending and under examination.

2. The rejection of claim 136 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in response to Applicant's amendment to the claim filed on 10/02/2007.

Upon further consideration, all rejections pertaining to claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142 and 144-146 are withdrawn in favor of a new rejection as set forth below.

Note: Change in Art Unit and SPE

The Examiner of record is now Ileana Popa, Art Unit 1633. Therefore, future correspondence should reflect such changes. Also, at the end of the Action is the information regarding the SPE and the Art Unit.

Double Patenting

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees.

A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1, 5-9, 12, 15-18, 22, 129, 135-137, 139-142 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 4, 5, and 9-14 of copending Application No. 10/300,247. Although the

conflicting claims are not identical, they are not patentably distinct from each other because they are obvious variants.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are drawn to a method of inducing a mucosal immune response by administering to a subject an oligonucleotide 8 to 100 nucleotides long and a viral antigen not encoded by a nucleic acid; the oligonucleotide has the formula 5' $X_1X_2CGX_3X_4$ 3', wherein C is unmethylated, X_1, X_2, X_3, and X_4 are nucleotides, and both the oligonucleotide and the antigen are administered intranasally or ocularly (claims 1, 22, 129, 135-137, and 139-142). The antigen is delivered in colloidal dispersion systems (claims 5-7), the method further comprises administering a non-oligonucleotide adjuvant, such as MPL (claims 8 and 9), the subject is at risk of developing an infectious disease (claim 12), the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end (claims 15-17), X_1X_2 could be GpT and X_3X_4 could be TpT (claim 18). The specification defines that the viral antigen could be a hepatitis B viral antigen and therefore, the vaccine could be used to elicit an immune response in a subject infected with hepatitis B therefore, i.e., the vaccine can be used to treat a subject infected with hepatitis B (p. 27, lines 14-23, p. 29, line 14, p. 40, lines 13 and 14).

The application claims recite a method of treating a subject infected with hepatitis via inducing an immune response against hepatitis virus by administering to the subject an oligonucleotide 8 to 100 nucleotides long, an antigen, and a non-nucleic acid adjuvant (claims 1, 4, and 12), wherein the non-nucleic acid adjuvant could be MPL

(claim 5); the oligonucleotide has the formula 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated, X_1, X_2, X_3, and X_4 are nucleotides, the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end (claims 9-11 and 13), X_1X_2 could be GpT and X_3X_4 could be TpT (claim 14). The specification defines that the antigen could be a polypeptide (i.e., not encoded by a nucleic acid vector), the non-nucleic acid adjuvant could be a liposome (i.e., micellar, lipid-based system), and that the delivery could be intranasal or ocular (p. 3, lines 11 and 12, p. 16, lines 5-13, p. 27, lines 16 and 17).

Since the application claims embrace all the limitations of the instant claims, the application claims and the instant claims are obvious variants.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1, 4-9, 12, 13, 15-20, 22, 25-28, 129, 135-142, and 144-146 are rejected under 35 U.S.C. 103(a) as being unpatentable over Krieg et al. (U.S. Patent No. 6,239,116, of record) in view of each Agrawal et al. (U.S. Patent No. 6,426,334, of record), Briles et al. (U.S. Patent No. 6,042,838, of record), Craig (U.S. Patent No. 6,689,757, of record), Kincy-Cain et al. (Infection and Immunity, 1996, 64: 1437-1440), and Berzofsky et al. (U.S. Patent No. 6,749,856).

Krieg et al. teach a method of inducing a mucosal immune response in a subject by orally administering to the subject an oligonucleotide 8 to 100 nucleotides in length, wherein the oligonucleotide can be administered by itself or concurrently with an antigen; the oligonucleotide has a sequence which includes the formula 5' $X_1X_2CGX_3X_4$ 3' wherein C is unmethylated, X_1, X_2, X_3, and X_4 are nucleotides, the oligonucleotide contains phosphorothioate modifications at the 5' end or the 3' end, X_1X_2 could be GpT, and X_3X_4 could be TpT (claims 1, 4, 15-18, 136-139, and 141) (Abstract, column 6, lines 1-67, column 7, column 14, lines 3-32, column 28, lines 4-25, column 45, lines 36-42, column 46, lines 55-60). Krieg et al. teach that the administration of the oligonucleotide by itself results in an immune response; such an immune response would protect a subject from subsequent passive exposure to antigen (claim 138) (columns 6, lines 38-51). Krieg et al. teach that a non-oligonucleotide adjuvant could be included in the immunogenic composition (claim 8), that the antigen could be a protein, i.e., not encoded by a nucleic acid vector (claims 1, 20, 136, 137, 139, 141, 142, and 144-146) (column 7, lines 1-7, column 9, lines 48-53), and that the method could be used to induce an immune response in subjects to eliminate tumors or viral infections (claims 12, 13, 135, and 140) (column 10, lines 23-61). Krieg et al. teach administering the composition in conjunction with liposomes (claims 5-8) (column 13, lines 40-45, column 45, lines 6-17). Krieg et al. teach their oligonucleotide as having the formula 5' TCCATGTCGTTCCTGTCGTT3' (SEQ ID NO: 73), i.e., comprising the sequence 5' $TCNTX_1X_2CGX_3X_4$ 3' wherein N is 2 (claim 19) (column 32, Table 10). Krieg et al. also teach boosting with oligonucleotide to enhance the immune responses to the vaccines

(claim 27) (column 47, lines 10-29). With respect to the limitation recited in claim 28, it would have been obvious to one of skill in the art to include the non-nucleic acid adjuvant in the boost in order to improve the results.

Krieg et al. do not teach specifically the recited routes of administration recited in the instant claims 1, 136, 137, 139 and 141. However, at the time of filing such administration routes were taught by the prior art. For example Agrawal et al. teach inducing a mucosal immune response by administering oligonucleotides having a sequence including the claimed formula via intranasal or rectal administration (claims 1, 136, 137, 139, and 141) (column 5, lines 30-45, column 6, lines 48-50). It would have been obvious to one of skill in the art, at the time the invention was made, to substitute the oral administration of Krieg et al. with the intranasal or rectal administration of Agrawal et al. to achieve the predictable result of inducing mucosal immunity.

Although Krieg et al. and Agrawal et al. do not specifically teach that intranasal immunization results in mucosal immunity at remote sites (claim 26), this is an inherent feature of their method because the prior art teaches that intranasal administration results in mucosal immunity at remote sites. For example, Briles et al. teach that intranasal administration of antigens together with adjuvants results in induction and secretion of specific IgA antibodies in the digestive and genital tracts, i.e., remote mucosal immunity (column 8, lines 14-24, Examples).

Although Krieg et al. and Agrawal et al. teach the use of non-nucleic acid adjuvants, they do not specifically teach the adjuvants recited in claim 9. However, at the time the invention was made, such adjuvants were well known and used in the prior

art. For example Briles et al. teach the use of saponins or cholera toxin and its B subunit (column 4, lines 20-30, column 8, lines 14-18). It would have been obvious to one of skill in the art to use an adjuvant such as cholera toxin in the method of Krieg et al. and Agrawal et al. to achieve the predictable result of eliciting an immune response.

Krieg et al., Agrawal et al., and Briles et al. do not teach administering B-7 costimulatory molecule (claim 25). Craig teaches using B-7 to upregulate the immune response to vaccines (column 6, lines 35-49). Therefore, it would have been obvious to one of skill in the art, at the time the invention was made, to modify the method of Krieg et al., Agrawal et al., and Briles et al. by further using B-7 costimulatory molecule, with a reasonable expectation of success. One of skill in the art would have been motivated to do so in order to enhance the immune response elicited against the vaccine of interest. One of skill in the art would have been expected to have a reasonable expectation of success in doing such because the art teaches that B-7 can be successfully used to potentate the immune responses to antigens.

With respect to the limitation recited in claim 129, it is noted that Krieg et al. teach their oligonucleotide as being capable of inducing IL-12 (column 6, lines 1-51, column 35, lines 50-67). The prior art teaches that IL-12 induces mucosal immune responses against intracellular pathogens ant it is useful as a mucosal adjuvant for vaccines used to prevent or treat infectious with pathogens which gain entry via a mucosal surface (see Kincy-Cain et al., Abstract, p. 1437, column 1, second paragraph, p. 1439, column 2; Berzofsky et al., Abstract, column 3, lines 1-9, column 12, lines 36-50). Based on these teachings, one of skill in the art would have known that the

oligonucleotide of Krieg et al. is a mucosal adjuvant which could be used to treat subjects in need of mucosal immunization.

Thus, the claimed invention was *prima facie* obvious at the time the invention was made.

Applicant's arguments are answered below to the extent that they pertain to the instant invention.

Applicant argues that although the Examiner states that intranasal and rectal administrations have both been routinely and successfully used for delivering of synthetic oligonucleotide containing an unmethylated CpG motif to induce an immune response in an infected subject or a tumor bearing subject, the working examples of Agrawal et al. employ non-mucosal routes. Additionally, Applicant argues that the combination suggested by the Examiner does not result in every limitation of the rejected claims. Each of the rejected claims requires administration to a subject in need of a mucosal immune response. None of the cited references teaches treatment of subjects in need of a mucosal immune response. None of the references even teaches that mucosal routes of administration are preferable over non-mucosal routes. For example, the working examples of Agrawal et al. employ either intraperitoneal or subcutaneous administration which are not mucosal administration routes, and there is no evidence that they induce a mucosal immune response and that the subjects to whom the oligonucleotides were administered were in need of such a response. As taught in the specification, a mucosal immune response is characterized by the

presence of sIgA in mucosal tissues. This immune response is not a systemic immune response. Agrawal et al. teach a method for inducing systemic IL-12 levels. The Examiner has not provided any evidence that the IL-12 immune response taught by Agrawal et al. is a mucosal immune response. Applicant submits that Craig et al. do not cure the deficiencies in the combination of Krieg et al. and Agrawal et al. Moreover, Applicant argues, Craig et al. requires dual delivery of an epitope (or antigen) in its peptide or polypeptide form and a nucleic acid encoded epitope (or antigen). Claims 1,136-139 and 144 all explicitly recite that the antigen is not encoded in a nucleic acid vector. The combination of these references therefore yields a method that requires administration of nucleic acid that encodes an epitope (or antigen); the claims specifically exclude such a limitation. Accordingly, the combination does not yield each and every limitation of the claim, and a *prima facie* case has not been made and therefore, Applicant requests the withdrawal of the rejection.

Applicant's arguments are acknowledged, however, they are not found persuasive for the following reasons:

Applicant's argument that the working examples of Agrawal et al. employ non-mucosal routes is irrelevant because Agrawal et al. do disclose intranasal and intrarectal routes of administration as suitable to deliver CpG motif-containing oligonucleotides to induce immune responses. Therefore, one of skill in the art would have known that intranasal or intrarectal administration work as well as the oral route of Krieg et al. and would have known to use them in the method of Krieg et al. to achieve a predictable result, i.e., enhancing immune responses to antigens. Applicant argues that

none of the references even teaches that mucosal routes of administration are preferable over non-mucosal routes. In response to this argument, it is noted that the mucosal route is already taught by Krieg et al. and therefore, there is no need of a motivation to change their method. Applicant also argues that the Examiner has not provided any evidence that the IL-12 immune response taught by Agrawal et al. is a mucosal immune response. However, it is noted that the teachings of both Kincy-Cain et al. and Berzofsky et al. clearly demonstrate that IL-2 induces a mucosal immune response and it can be used to treat subjects in need of mucosal immunization. With respect to Craig, it is noted that the reference was cited for teaching the B-7 costimulatory molecule (see above). It is the teaching of B-7 as an immune response stimulator that would have made one of skill in the art to use it in the method of Krieg et al. and Agrawal et al., i.e., one of skill in the art would have used the antigen of Krieg et al. and Agrawal et al. (i.e., an antigen not encoded by a nucleic acid vector) in conjunction with the B-7 disclosed by Craig. Therefore, Applicant's argument that the combination of these references yields a method requiring administration of nucleic acid that encodes an epitope (or antigen) is not found persuasive. For these reasons, the rejection is maintained.

7. No claim is allowed. No claim is free of prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ILEANA POPA whose telephone number is (571)272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on 571-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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